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EXAMINER	
TON, THAIAN N	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,183	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19,24,25,29-32,34,39-43 and 45-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19,24,25,29-32,34,39-43 and 45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Remarks and Response, filed 6/20/08, have been entered. Claims 17, 39, 46 and 47 are amended; claim 49 is cancelled; claims 17, 19, 24, 25, 29-32, 34, 39-43, 45-48 are pending and under current examination.

Information Disclosure Statement

Applicants' IDS, filed 8/8/08, has been considered

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17, 19, 24, 25, 34, 39-42 and 45-48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kalka et al (Angiogenesis and Vasculogenesis, Heart, Urban and Vogel, Vol.25, No.6, pages 611-622, 2000) and Chiu et al (US2002/0197240).

Applicants' Arguments. Applicants argue that Kalka in combination with Chiu do not arrive at the claimed invention because Kalka does not teach or suggest the use of early attaching cells obtains by culturing bone marrow as gene therapy expression cells for delivering to ischemic muscle tissue one or more angiogenic agents that enhance development of collateral blood vessel supply, wherein the angiogenic agent(s) are expressed by the early attaching cells in vitro. Applicants argue that the Examiner fails to document that the initial population of EPCs in the early attaching cells obtained by culturing bone marrow was known to those of skill in the art was to be substantially greater than that which can be extracted from

peripheral blood circulation, and that Applicants submit that it was not known in the art, nor does the Examiner provide evidence showing, that bone marrow cells extracted from peripheral circulation are substantially "the same" as those extracted from peripheral blood circulation or would suggest use of those obtained by culturing bone marrow. Applicants argue that it was well known that PECs, such as those disclosed by Kalka, are influenced in their development by the in vivo environment in which they are found, and that the bone marrow cells used in the experiments described by Kalka are not identified as autologous to the patient treated. See pp. 7-8 of the Response.

Response to Arguments. These arguments have been fully considered but are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, it is the combination of references that arrive at the claimed invention. Although Kalka do not teach using autologous bone marrow, this teaching and suggestion is clearly present in Chiu (see, for example, p. 4, ¶51), which discuss utilizing autologous bone marrow stroma cells. With regard to Applicants' arguments that Kalka are silent regarding "further culturing" of the transfected early attaching cells to express into a conditioned media, it is noted that the claims, as written, are directed to "cells obtained by culturing autologous bone marrow", which is not considered an active step in the method steps. Similarly, Applicants argue that Kalka is silent regarding a method for enhancing collateral blood vessel formation in heart or limb muscle tissue by injecting into such tissue a composition that will contain expressed transgenic anigiogenic factors, and they do not suggest the invention method recited by claim 47, where bone marrow cells are used as expression cells for producing in vitro a transgenic stimulatory angiogenic

factor to "jump start" the cells in a cascade of endogenous angiogenic factors that blood marrow-derived cells were known to produce when implanted in ischemic tissue. Applicants argue that with regard to "therapeutic angiogenesis," Kalka fail to enable a method involving injection of transfected bone marrow cells of any provenance because they only describe expression of a marker protein transfected by EPCs, and only suggest the possibility of postnatal neovascularization, therefore, Applicants argue that that Kalka reference would prohibit a well-founded belief in the success of such a method, if those of skill in the art were motivated "to try" administration of recombination EPCs for any type of adult angiogenesis for therapeutic purposes. Applicants argue that even if one of skill in the art were motivated by the disclosure of Kalka to try substitution of transgenic cells, Applicants argue that Kalka fails to constitute obviousness under the statute because the requisite expectation of success is missing, and indeed warned against. See pages 8-9 of the Response.

The phrase that the cells are "obtained by culturing autologous bone marrow" is not considered an active step in the claims; therefore, any art that teach utilizing early attaching cells would fulfill the limitation of the claims. Additionally, Kalka teach that the EPCs are isolated from peripheral blood which is originated from bone marrow (p. 18, last ¶ and pp. 23-24); therefore, because they teach the same source (bone marrow) as the instant invention, it is maintained that there is a reasonable expectation of success that Kalka's cells would have the properties as those found in the instant claims. With regard to the limitation of claim 47, it is noted that Chiu is relied upon for the limitation that the cells are transfected with an adenoviral vector encoding one or more of the angiogenic factors such as HIF-1, EPAS1, MCP-1 GM-CSF, etc. Additionally, it would also have been obvious to one of ordinary skill in the art to use early attaching cells transfected with adenoviral vector encoding angiogenesis factors such as HIF1 or GM-CSF and injecting a composition that comprises angiogenic factors in the conditioned medium to

enhance collateral blood formation in heart or limb muscle based on the combined teaching of Kalka et al and Chiu (claims 47, 17 and 49). As discussed above, factors such as GM-CSF would enhance migration of EPC to the damaged site, and HIF1 would induce angiogenic gene expression of the cell. As such, one of ordinary skill in the art would inject the cell and composition together because the combined effect of the cells expressing an angiogenic factor and the direct injection of such factor would enhance the collateral blood vessel formation in the ischemic site. The ordinary artisan would also be able to determine the amount of composition and how many sites would need injection based on the amount of angiogenic factor in the medium and where the damaged sites are, and such determination would have been routine experimentation.

With regard to Kalka's teachings, it is noted on p. 26, that Kalka teaches, "The positive of EPC on the neovascularization through transfection of these cells with growth factors could be reinforced for the treatment of an ischemia." Thus, Kalka provide clear suggestion for the claimed invention. Kalka further teach that utilizing an EPC transfected with an adenoviral vector encoding VEGF show new formation of vessels and an increase of EPC circulating in the blood (see pages 26-27, bridging sentence). Therefore, Kalka clearly teaches that using growth factors, they found neovascularization and suggest their techniques for therapeutic purposes.

With regard to claim 46, it is noted that the claims discuss an intended use that does not impart patentable weight. Intended used does not impart patentable weight to a product. See MPEP 2111.03:

> Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re

Casey 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459, (CCPA 1963).

See also, MPEP 2111.02(II) also, which recites, "If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim. See, e.g., In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997)" and 2112-2112.01.

Applicants' Arguments. Applicants argue that the Examiner's reliance on Chiu does not provide obviousness to the claimed invention because Chui pertains primarily to myogenesis, not angiogenesis, and that they disclose injection into an MI patient autologous marrow stromal cells that have been modified to express a cardiomyocyte phenotype in vitro. Thus, the therapeutic goal of Chiu is myogenesis, not angiogenesis, as in the claimed method. Applicants argue that Chui's secondary group of marrow stromal cells are non-modified, and therefore, they do not suggest transfection of angiogenesis-producing cells. Applicants argue that Chui is silent regarding the use of transfected cells from culture of bone marrow cells for any purpose, and therefore do not contemplate transfection of MSCs with any therapeutic angiogenic factor, let alone one that will be expressed in vitro for administration to a subject in conditioned medium. See p. 10 of the Response.

Response To Arguments. These arguments have been fully considered but are not persuasive. In particular, it is the combination of Kalka and Chiu that arrive at the claimed invention. Kalka teach methods for enhancing collateral blood vessel formation utilizing EPCs transfected with an adenoviral vector encoding angiogenic factor VEGF. Therefore, Kalka provide sufficient guidance with regard to the specific cell type as that instantly claimed, and further, that utilizing a vector encoding an angiogenic factor. Although Kalka does not specifically teach the angiogenic factors that are instantly claimed, it would have been readily apparent to the skilled artisan that angiogenic factors are well-known. Additionally, since EPC and bone marrow stromal cells are a large part of the early attaching cells

isolated from bone marrow, and both of them has angiogenic effect in tissue repairing, it would have been obvious to one of ordinary skill in the art to use such combined population of cells in the method of enhancing collateral blood vessel formation, especially because EPC from peripheral blood is very rare. Since Kalka et al. already demonstrated that EPC expressing angiogenic factor VEGF increased collateral blood formation, it would have been obvious to an ordinary artisan that transfecting other types of angiogenic factor such as GM-CSF or HIF1 to this early attach cell population because all of these factors are stimulant of blood vessel formation. Further, expression of GM-CSF would also induce EPC migration to the damaged site. Accordingly, the prior rejection of record is maintained.

Rejection

Kalka et al. teach a method for enhancing collateral blood vessel formation in hind limb muscle by using EPC transfected with an adenoviral vector encoding angiogenic factor VEGF (see translation page 26 last paragraph through page 27 1st paragraph). Kalka et al. also teach that EPC isolated from peripheral blood are originated from bone marrow, and they are able to enhance collateral blood vessel formation in hind limb in animal model (see page 18, last paragraph, and page 23-24). Kalka et al. also teach that an essential stimulus for blood vessel formation is a lack of oxygen, and hypoxia induced transcription factors such as HIF-1 are modulators for this process (see page 4, 2nd paragraph). Kalka et al. further teach that cytokine such as GM-CSF acts as a stimulant of the migration of EPC *in vitro*, and results in multiplication of EPC *in vivo*.

However, Kalka et al. do not teach a method for enhancing collateral blood vessel formation by using early attaching cells obtained from bone marrow transfected with an adenoviral vector encoding one or more of the angiogenic factors such as HIF-1, EPAS1, MCP-1 GM-CSF, etc.

Chiu teach a method of implanting bone marrow stromal cells to patients suffering from myocardial infarction and heart failure, and wherein such

implantation results in not only repopulation of the myocytes surrounding the scar tissue, but also contribute to the collateral blood vessel formation by differentiates into endothelial tubes and smooth muscle fibers (see page 12, [0161]). Chiu et al. also teach such cells may be injected to multiple sites within the damaged area of the tissue (page 12, [0161]).

It would have been obvious to one of ordinary skill in the art to use early attaching cells transfected with adenoviral vector encoding angiogenesis factors such as HIF1 or GM-CSF to enhance collateral blood formation in heart or limb muscle based on the combined teaching of Kalka et al and Chiu. Since EPC and bone marrow stromal cells are a large part of the early attaching cells isolated from bone marrow, and both of them has angiogenic effect in tissue repairing, it would have been obvious to one of ordinary skill in the art to use such combined population of cells in the method of enhancing collateral blood vessel formation, especially because EPC from peripheral blood is very rare. Since Kalka et al. already demonstrated that EPC expressing angiogenic factor VEGF increased collateral blood formation, it would have been obvious to an ordinary artisan that transfecting other types of angiogenic factor such as GM-CSF or HIF1 to this early attach cell population because all of these factors are stimulant of blood vessel formation. Further, expression of GM-CSF would also induce EPC migration to the damaged site. Since Kalka et al. already demonstrated that transfecting EPC cells with adenoviral vector encoding VEGF increased blood vessel formation in hind limb of an animal model, one of ordinary skill in the art would have reasonable expectation of success to introduce other types of angiongenic factor carried by adenoviral vector to the early attaching cells which comprises EPC, and injecting to the site with impaired blood flow to enhance collateral blood flow. Moreover, the ordinary artisan would also be motivated to stimulate the transfected cell by hypoxia *in vitro* because it is well known that it will induce the expression of genes responsible for angiogenesis as taught by Kalka et al. Therefore, the invention

would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

It would also have been obvious to one of ordinary skill in the art to use early attaching cells transfected with adenoviral vector encoding angiogenesis factors such as HIF1 or GM-CSF and injecting a composition that comprises angiogenic factors in the conditioned medium to enhance collateral blood formation in heart or limb muscle based on the combined teaching of Kalka et al and Chiu (claims 47, 17 and 49). As discussed above, factors such as GM-CSF would enhance migration of EPC to the damaged site, and HIF1 would induce angiogenic gene expression of the cell. As such, one of ordinary skill in the art would inject the cell and composition together because the combined effect of the cells expressing an angiogenic factor and the direct injection of such factor would enhance the collateral blood vessel formation in the ischemic site. The ordinary artisan would also be able to determine the amount of composition and how many sites would need injection based on the amount of angiogenic factor in the medium and where the damaged sites are, and such determination would have been routine experimentation. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 29-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kalka et al (Angiogenesis and Vasculogenesis, Heart, Urban and Vogel, Vol.25, No.6, pages 611-622, 2000) and Chiu et al (US2002/0197240) as applied to claims 17, 19, 24, 25, 34, 39-42 and 45-48 in further view of Hamawy et al, Smith et al. and Li et al.

Response to Arguments. Applicants' arguments regarding Kalka and Chiu are addressed above. Applicants argue that the Examiner has failed to point out any passages in Hamawy, Smith or Li, other than those disclosing yet another angiogenic factor endogenous produced by an individual suffering from ischemic

muscle tissue, that would overcome the differences between the combined disclosures of the primary references, thus, Applicants argue that the cited art fails to establish a *prima facie* case of obviousness. The arguments regarding the primary references have been discussed above and thus, the rejection is maintained.

The teaching of Kalka et al. and Chiu et al. are discussed above. However, they do not teach angiogenic factors such as FGF, NOS or PR39.

Hamawy et al. teach that over 20 angiogenic factors are identified in the prior art in discussing therapeutic angiogenesis and gene therapy strategies for revascularization of ischemic muscle tissue (e.g., myocardial) (e.g., p. 516, col. 2, Table 1). Indeed, the list of angiogenic factors includes the VEGF that Kalka teaches, as well as FGF(s) as recited in claim 39. Furthermore, Hamawy discusses that gene therapy vectors can include several well-characterized systems, including that of adenovirus. (e.g., p. 517, Table 2, and col. 2, last ¶ bridging to p. 518).

There are also evidence in the prior art teaches that said NOS and PR39 proteins are recognized as factors that promote angiogenesis. For example, Smith teaches a method of utilizing an NOS-encoding adenovirus vector in a method of promoting angiogenesis in a rat model of hind limb ischemia. (e.g., Abstract; p. 1280, col. 1, under Methods; p. 1282, Fig. 2; p.1283, col. 2, ¶ 2). The salient teaching is that NOS is one of yet another host of angiogenic factors.

In addition, Li teaches that the peptide PR39 through its effects on HIF1 protein vis-h-vis preventing degradation results in promotion of collateral blood vessel formation. (e.g., Abstract;
p. 49, col. 2, ¶ 2; p. 50, col. 2; p. 52, Fig. 3). Once again, the salient teaching is that PR39 is another angiogenic factor that is shown to promote angiogenesis.

Therefore, it would have been obvious to modify the adenoviral vector encoding VEGF as taught by Kalka, to instead encode either FGF, NOS or PR39 as taught by Hamawy, Smith and Li, respectively. One would have been motivated to make such modification to extend the range of therapeutic angiogenic factors in a

method of treating muscle ischemia using early attaching cells from bone marrow as taught by Kalka and Chiu. Further, given the level of skill in the art at the time of invention there would have been a reasonable expectation of success in replacing one angiogenic factor with another.

Claim 43 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kalka et al (Angiogenesis and Vasculogenesis, Heart, Urban and Vogel, Vol.25, No.6, pages 611-622, 2000) and Chiu et al (US2002/0197240) as applied to claims 17, 19, 25, 34, 39-42, 45, 46 and 48, in further view of Tomika.

Response to Arguments. Applicants provide the same arguments as above, regarding Kalka and Chiu. These arguments have been addressed above and are maintained.

The teaching of Kalka et al. and Chiu et al. are discussed above. However, they do not teach a therapeutic composition comprising the claimed early attaching cells and an anti-coagulant.

Tomita et al. teach that obtaining bone marrow derived cells (i.e., through aspiration) it is beneficial to have an anticoagulant present. (e.g., p. 247, col. 2, last ¶ bridging to p. 248).

Therefore, in obtaining bone marrow derived cells for *ex vivo* expansion, it would have been obvious to add heparin to the aspirate so as to obtain the benefit of preventing coagulation/clotting of cells in the marrow aspirate, as is taught by Tomita. Given the level of skill in the art at the time of invention, it would have been obvious to add the component of an anticoagulant to a composition comprising bone marrow, which in turn comprises cells that are expanded/transfected *ex vivo*.

Claim Rejections - 35 USC § 112

The prior rejection of claims 45 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants' amendment to the claims, which now recite that the cells are "obtained by culturing bone marrow aspirated from the patient."

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632